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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,364	07/05/2001	Paul D. van Poelje	MET-037CXT	7049

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/900,364	VAN POELJE ET AL.	
	Examiner	Art Unit	
	YONG S. CHONG	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 115-179* is/are pending in the application.

4a) Of the above claim(s) *123,125,127,128,141-144 and 147-179* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 115-122, 124, 126, 129-140, 146-146* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

Claim(s) 2-114 have been cancelled. Claim(s) 123, 125, 127-128, 141-144, 147-179 have been withdrawn. Claim(s) 1, 115-179 are pending. Claim(s) 1, 115-122, 124, 126, 129-140, 145-146 are examined herein.

Applicant's arguments have been fully considered but found not persuasive. The rejection(s) of the last Office Action are maintained for reasons of record and repeated below for Applicant's convenience.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 115-122, 124, 126, 129-140 and 145-146 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 51-55 of U.S. Patent No. 6965033. Although the conflicting claims are not identical, they are not patentably distinct from each other because current claim 1 is drawn to a pharmaceutical composition comprising at least one insulin secretagogue and a FBPase inhibitor selected from the group of formula I or IA, and '033 claim 51 is drawn to a method of treating diabetes comprising administering a compound of formula I (wherein formula I is equivalent to the compunds of currently claimed formula I and IA). As the '033 patent uses the open language "comprising" additional antidiabetic compounds can be administered including sufonylureas such as glyburide.

Claims 1, 115-122, 124, 126, 129-140 and 145-146 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6756360. Although the conflicting claims are not identical, they are not patentably distinct from each other because current claim 1 is drawn to a pharmaceutical composition comprising at least one insulin secretagogue and a FBPase inhibitor selected from the group of formula I or IA, and '360 claim 1 is drawn to a pharmaceutical composition comprising an insulin sensitizer agent and an FBPase inhibitor. In '360 claim 4 the FBPase inhibitor is a compound selected from the formula I and IA wherein formula I and IA are identical to the formula I and IA of the current claim 1. Further glyburide is a known insulin sensitizer and secretagogue.

Response to Arguments

The response to arguments with respect to the obviousness-type double patenting rejections above will be addressed with the 103(a) obviousness rejection below since Applicant's arguments are relevant in both rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 115-122, 124, 126, 129-140 and 145-146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erion et al. (US Patent No. 6,756,360) in view of Weber et al. (US Patent No. 3,454,635).

The applied reference has a common assignee and inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Erion et al. teach, in the abstract, pharmaceutical compositions containing an FBPase inhibitor and an insulin sensitizer, as well as methods for treating diabetes and diseases responding to increased glycemic control, improved insulin sensitivity, a

reduction in insulin levels, or an enhancement of insulin secretion. In col. 4 lines 45-50, Erion et al. teach that an aspect of the invention is to use FBPase inhibitors in combination with insulin sensitizer therapies that include administration of agents that enhance endogenous or exogenous insulin levels, such as sulfonylureas, insulin, or insulin mimetics. In col. 190 lines 1-20, Erion et al. teach a particular FBPase inhibitor used in their biological assays called Compound J. The Compound J detailed in the '630 patent is identical to the currently claimed compound J.

Erion et al. does not teach the use of Compound J with the particular sulfonylurea antidiabetic glyburide.

Weber et al. teach, in col. 1 line 20 to col. 2 line 5, benzenesulfonyl ureas having hypoglycemic activity of the formula detailed in lines 22-28. In col. 5 lines 5-75, Weber et al. teach compound IV (glyburide) as having strong hypoglycemic action when administered orally. The compound can be used in the manufacture of orally administrable pharmaceutical preparations for the lowering of blood sugar in the treatment of diabetes mellitus and can be used in their pharmaceutically acceptable salt forms. The compositions can be in the forms of tablets with a suitable pharmaceutically acceptable carrier and can be given in dosage per unit amounts to 0.5-100mg but higher and lower dosages can be utilized.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use glyburide in combination with a FBPase inhibitor, as Erion teaches such a combination. Further Erion et al. disclose Compound J as an FBPase inhibitor in the '630 patent and this compound is the same Compound J as currently

claimed. Compound J is taught as useful in the treatment of diabetes and glyburide is a known antidiabetic agent.

The examiner respectfully points out the following from MPEP 2144.06: "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re* Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 1, 115-122, 124, 126, 129-140 and 145-146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jiang et al. (US Patent No. 6,965,033) in view of Weber et al. (US Patent No. 3,454,635).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention “by another”; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the

application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Jiang et al. teach, in the abstract, novel bisamidate phosphonate prodrugs of FBPase inhibitors of formula IA and their use in the treatment of diabetes and other conditions associated with elevated blood glucose. Jiang et al. teach, in col. 29 line 5 to col. 31 line 55, compounds of formula i, wherein R^{55} can be moiety 1 of group1; A can be NH_2 (moiety 1); B can be –iBu (moiety 2); Q^1 and Q^2 can both be moiety 2; and R^{14} can be OEt. This gives Compound J of the currently claimed application.

Jiang et al. does not teach the use of the FBPase inhibitor specified above in conjunction with the antidiabetic sulfonylurea glyburide.

Weber et al. teach, in col. 1 line 20 to col. 2 line 5, benzenesulfonyl ureas having hypoglycemic activity of the formula detailed in lines 22-28. In col. 5 lines 5-75, Weber et al. teach compound IV (glyburide) as having strong hypoglycemic action when administered orally. The compound can be used in the manufacture of orally administrable pharmaceutical preparations for the lowering of blood sugar in the treatment of diabetes mellitus and can be used in their pharmaceutically acceptable salt forms. The compositions can be in the forms of tablets with a suitable pharmaceutically acceptable carrier and can be given in dosage per unit amounts to 0.5-100mg but higher and lower dosages can be utilized.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use glyburide in combination with a FBPase inhibitor, as Jiang et al. teach that FBPase inhibitors are useful in the treatment of diabetes and Weber discloses that sulfonylureas are antidiabetic agents. Further Jiang et al. disclose an FBPase inhibitor identical to currently claimed Compound J. Compound J is taught as useful in the treatment of diabetes and glyburide is a known antidiabetic agent.

The examiner respectfully points out the following from MPEP 2144.06:
"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re* Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Response to Arguments

Applicant argues nonobviousness by claiming unexpectedly superior results for the combination of Compound J and glyburide when used in the treatment of diabetes as compared to the administration of either compound alone. Specifically, Applicant draws attention to Example X, where enhanced reduction in the area under the curve of blood glucose during the initial 4 hours post drug administration. Additionally, the combination treatment attenuated an increase in blood lactate levels that were observed in the compound J monotherapy group. These results are more pronounced in chronic groups. Further, Example Y indicates that the combination of glyburide and Compound

J resulted in greater glucose lowering than either Compound J or glyburide alone in chronic ZDF rats that were treated.

This is not persuasive because, at the outset, none of the results in Example X or Y reflect unexpected superior results for the combination of Compound J and glyburide when used in the treatment of diabetes as compared to the administration of either compound alone, but rather, shows therapeutically additive effects of combining two known active agents for the same purpose. More specifically in Table 11 and Figure 1, Examiner does not view going from 1121 (glucose AUC) for Compound J to 895 (glucose AUC) for Compound J and glyburide as unexpected superior results, especially with such high error bars. With respect to the blood lactate levels in Figure 2, there does not seem to be any unexpected results since the graph for the combination of Compound J and glyburide is somewhere between the graphs for Compound J and glyburide. Furthermore, there is no data supporting the assertion that these results are more pronounced in chronic groups. Moreover, these results are not commensurate with the scope of the claims. Example X and Y administer defined amounts of Compound J and glyburide to ZDF rats, 300 and 100 mg/kg, respectively, however, claim 1 does not recite any limitation on amounts or dosages.

Regarding the establishment of unexpected results or synergism, a few notable principles are well settled. The Applicant has the initial burden to explain any proffered data and establish how any results therein should be taken to be unexpected and significant. See MPEP 716.02 (b). It is applicant's burden to present clear and convincing factual evidence of nonobviousness or unexpected results, i.e., side-by-side

comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art. The claims must be commensurate in the scope with any evidence of unexpected results. See MPEP 716.02 (d). With regard to synergism, a prima facie case of synergism has not been established if the data or result is not obvious. The synergism should be sufficient to overcome the obviousness, but must also be commensurate with the scope of the claims. Further, if the Applicant provides a DECLARATION UNDER 37 CFR 1.132, it must compare the claimed subject matter with the closest prior art in order to be effective to rebut a prima facie case if obviousness. See MPEP 716.02 (e).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

YSC

/SREENI PADMANABHAN/
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